University of Alberta

A Randomized Controlled Trial Comparing Propofol to Midazolam Plus Meperidine Sedation in Outpatient Colonoscopy

by

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Abstract

Background: Optimal sedation for adult outpatient colonoscopy remains to be defined.

Methods: 1) A systematic review was conducted to evaluate the evidence on propofol (P) compared to benzodiazepine/narcotic (B/N) sedation. 2) A randomized trial was conducted to compare recovery profile, patient satisfaction, procedure time, and adverse events of P versus midazolam plus meperidine (M+M) sedation.

Results: The systematic review revealed that P sedation resulted in a shorter recovery time compared to (B/N) sedation (by 14 minutes, 95% CI 9.90- 19.14), but the evidence was not definitive. Ninety-two patients were thus enrolled in this randomized trial. The median recovery time was significantly shorter in the P group (20 min) compared to the M+M group (45 min) ($p< 0.001$). The other outcomes were not significantly different between the two groups.

Conclusions: Propofol sedation is superior to M+M for outpatient colonoscopy in recovery profile. However, propofol sedation is not widely used due to institutional policies, financial constraints and manpower shortages.

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Chapter 1. Introduction: A Systematic Review on Propofol Sedation in Outpatient Colonoscopy

1.1. Background

Colonoscopy is an important diagnostic and therapeutic procedure. It is estimated that approximately 1.27 million colonoscopies are performed by gastroenterologists annually for colorectal cancer screening in the United States.[1] The total number of colonoscopies performed is much higher considering that many colonoscopies are performed for other indications.

Colonoscopy is an invasive procedure, not well tolerated by most patients if performed without sedation. There is considerable variability in the practice of sedation for endoscopic procedures worldwide. There are some centers which perform a significant proportion of gastroscopies and colonoscopies without sedation. On the other hand, general anesthesia is given to more than 90% of patients undergoing colonoscopy in France.[2] Most centers do use conscious sedation, usually in the form of benzodiazepines and/or narcotics, with propofol sedation reserved for difficult cases. Benzodiazepines and narcotics are effective and safe. However, the onset of sedation can be delayed, and in some patients conscious sedation is inadequate, resulting in a poor experience with the procedure. Moreover, there are significant post-sedation side effects, such as nausea, vomiting, and prolonged recovery period. [3] This can substantially increase procedure costs due to the need for prolonged monitoring after endoscopy.

Propofol, a general anesthetic agent, has been routinely used in various procedures and surgeries. It has a fast onset of action (within 30-60 seconds), a short half life (1.8-4.1 minutes)[4] but a narrow therapeutic window. The current package insert of propofol states that only persons trained in the administration of general anesthesia should administer propofol and these physicians should not be involved in the procedure so that patients can be continuously and properly monitored due to the risk of respiratory depression.[4] No deaths associated with propofol sedation have been reported since it was first introduced in gastrointestinal endoscopy in the mid 1980.[5] However, need for mechanical ventilation as a result of propofol sedation has been reported. In a number of small trials propofol was shown to have a superior recovery profile following various endoscopic procedures including gastroscopy, colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP).[6, 7] Indeed, propofol sedation is now used routinely in elective adult procedures in some centers. However, the lower cost of recovery is offset by the need for an anesthesiologist. Therefore, the use of propofol sedation is limited to selected endoscopic procedures or patients.

Although a number of small randomized trials have explored the efficacy of propofol sedation, the evidence is not definitive. Thus we conducted a systematic review to define what is known and what remains to be defined about propofol sedation for colonoscopy with regards to recovery profile, procedure time, patient satisfaction, safety and costs.

1.2. Methods

A literature search was conducted in Sept 2005 in the following electronic databases: MEDLINE (1966-2005), EMBASE (1988-2005), CINAHL (1982-2005), Cochrane Controlled Trials, DARE, LILACS, and Web of Science. Search terms included propofol, diprivan, gastrointestinal endoscopy, and colonoscopy. The search was limited to English language, human subjects, full text articles, and randomized controlled trials. In addition, reference lists of primary papers and review articles were hand searched. The inclusion criteria were: adult patients, elective colonoscopy, randomized trials, comparison between propofol and traditional sedation (ie a benzodiazepine, an opiate or a combination of both), and studies which reported recovery times, procedure times, adverse events, patient satisfaction and cost analysis. Studies were excluded if they were not randomized, included procedures other than colonoscopy, or did not compare propofol to usual sedation.

1.2.1. Study Selection and Data Extraction

Study selection, data extraction, and quality assessment of primary studies (based on whether there was concealment of allocation[8] and number of Jadad criteria[9] met) were performed by 2 independent reviewers. Discrepancies were resolved by consensus. The primary outcome for our review was recovery time after colonoscopy, defined by the interval between scope withdrawal and full recovery. We also collected data on total procedure times (defined as the interval between sedation administration and scope withdrawal), patient satisfaction scores, pain scores during procedures, adverse events and cost analysis.

1.2.2. Statistical Analysis

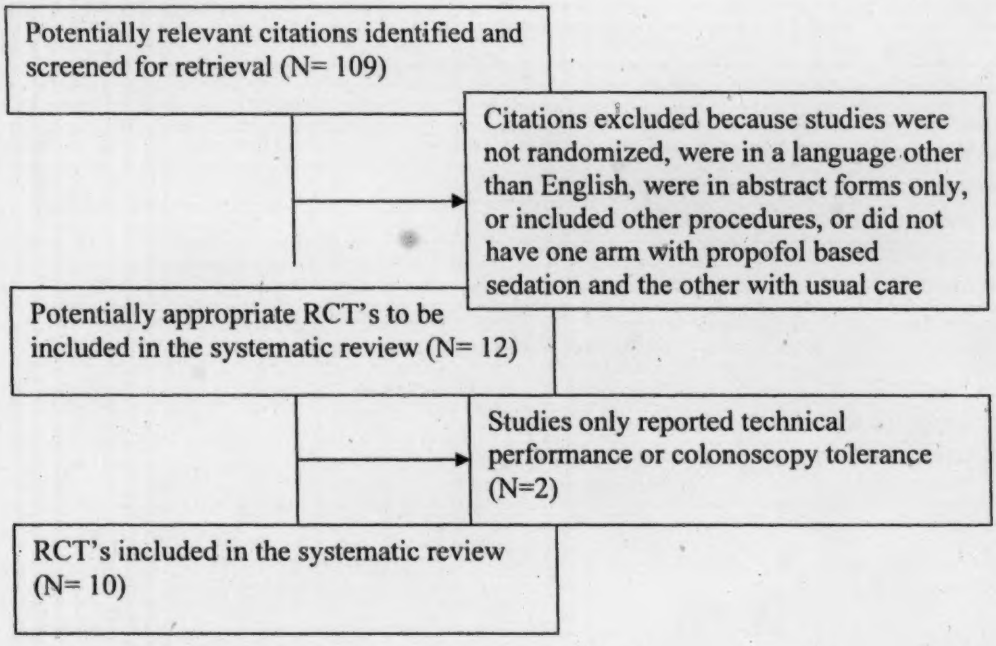
Post-procedure recovery times, total procedure times, patient satisfaction and pain scores were analyzed by quantitative methods. Adverse events and cost analysis were analyzed by descriptive methods. Random effects models were used to calculate summary effects and the I^2 value was used to evaluate statistical heterogeneity. Categorical data on patient satisfaction or pain scores were converted to a 4 point scale to facilitate statistical analysis.

1.3. Results

1.3.1. Results of Literature Search

A total of one hundred and nine titles were identified through the search of the databases listed below (Figure 1). Twelve studies met our screening criteria and were reviewed in full text. Ten randomized trials[10-19] met the inclusion criteria and were the subject of this systematic review.

Figure 1. Trial Flow



1.3.1. a) Study Characteristics

Three studies were from North America, five from Europe, and two from Asia. All of the studies were hospital based. The number of subjects in each study ranged from 40 to 120. Participants in the intervention arms were given propofol alone in 4 trials,[13, 14, 19] propofol with an opiate in 4 trials[10-12, 17] and propofol with a benzodiazepine in 2 trials.[15, 16] Participants in the control arms were given a combination of benzodiazepine and an opiate in 8 trials,[10-12, 15-19] a benzodiazepine alone in one trial,[14] and an opiate alone[13] in one trial. Propofol based sedation was administered by an anesthesiologist in three studies,[10, 13, 15] by patient controlled sedation (PCS) in four studies,[11, 12, 14, 17] by a non specialist physician in one study,[16] and by a registered nurse in two studies.[18, 19]

Table 1. Characteristics of Included Trials

Study	N	Intervention	Propofol Adminis-tration	Control(s)	Jadad Quality score	Concealment Of Allocation
Kostash[10] 1994	57	Propofol/fentanyl	anesthetist	Diazepam/meperidine Midazolam/fentanyl	5/5	Adequate
Roseveare[17] 1998	66	Propofol/alfentanil	PCS	Diazemuls/meperidine	2/5	Unclear
Reimann[16] 2000	79	Propofol/midazolam	Non specialist MD	Midazolam/nalbuphine	2/5	Unclear
Kulling[11] 2001	50	Propofol/alfentanil	PCS	Midazolam/meperidine	4/5	Unclear
Ng[14] 2001	88	Propofol	PCS	Midazolam	2/5	Adequate
Sipe[18] 2002	80	Propofol	Nurse	Midazolam/meperidine	4/5	Adequate
Paspatis[15] 2002	120	Propofol/midazolam	anesthetist	Midazolam/meperidine	2/5	Unclear
Lee[12] 2002	100	Propofol/alfentanil	PCS	Diazemuls/meperidine	3/5	Unclear
Ulmer[19] 2003	100	Propofol	Nurse	Midazolam/fentanyl	5/5	Adequate
Moerman[13] 2003	40	Propofol	anesthetist	Remifentanil	3/5	Unclear

PCS= patient controlled sedation

1.3.1. b) Methodological Quality of Included Studies

Two of the ten trials had a Jadad score of 3[12, 13], and 4 had a score of at least 4.[10, 11, 14, 15, 18, 19]The remaining four studies scored two on the Jadad scale. Allocation of concealment was adequate in four studies[10, 14, 18, 19] and was unclear in the remaining six.[11-13, 15-17]

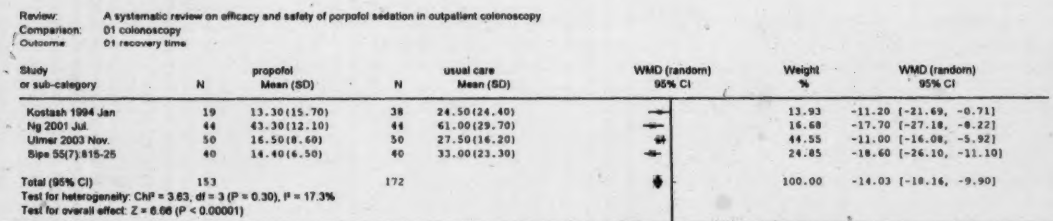
Baseline characteristics of participants, as well as inclusion and exclusion criteria were explicit in all included studies. One study did not report the number of participants in each treatment arm,[13] and therefore data from this study could not be used. In all studies, participants were recruited as outpatients scheduled to undergo colonoscopy. Eight of the ten trials reported the primary outcome of interest (ie. post-procedure recovery time).[10, 12-14, 16-19]However, there was considerable variability among studies with respect to how recovery was defined and how recovery time was reported. Four studies did not use a validated scale to define "full recovery".[12, 14, 16, 17] One studies used the Aldrete Scale,[10] two studies used the Observer's Assessment Scale[18, 19], and one study used the Steward Post Recovery Scale[13] to define recovery. The Aldrete scale was prospectively validated in assessing readiness to be discharge from the operating room following general anesthesia.[20] A minimum score of eight out of ten indicated that the patient was safe to retrun to the ward. The Observer's scale was validated for assessing recovery following benzodiazepine sedation.[21] Recovery time was assessed by individuals blinded to treatment assignment in six studies,[10, 12, 14, 16, 18, 19] not blinded in one study,[13] and unclear in the remaining studies.[11, 15, 17]

1.3.2. a) Recovery Times

Six of the eight trials reporting this outcome demonstrated statistically significantly shorter recovery time with propofol based sedation,[12, 14, 16-19] although only 4 of these 8 trials [14, 18, 19] reported means and standard deviations (these 4 trials are summarized in Figure 2). The remaining four studies reported medians, all demonstrated shorter median recovery times in the propofol based group: 0 min vs 5 min ($p<0.01$) in Lee's study, 0 min vs 3 min (p not given) in Moerman's study, 5 min vs 23 min ($p<0.001$) in Reimann's study, and 10 min vs 40 min ($p= 0.0001$) in Roseveare's study.[12, 13, 16, 17]

The pooled estimate suggested that propofol based sedation did shorten post-procedure recovery time by 14 minutes (95% CI 10 minutes to 18 minutes) (Figure 2).

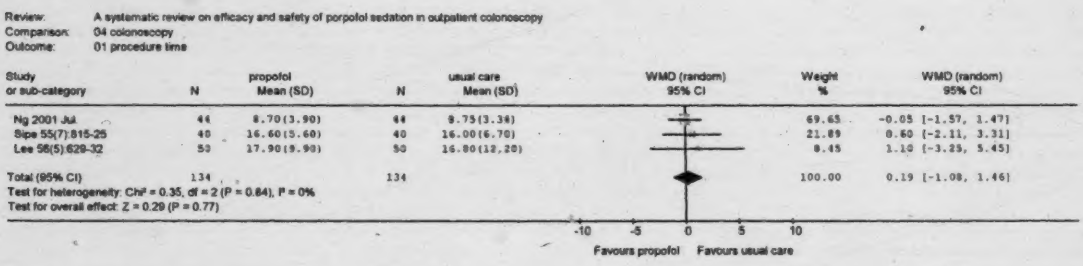
Figure 2 Recovery Time



1.3.2. b) Procedure Times

Of the 7 trials reporting this outcome,[12, 14-19] one reported no difference between the study groups without giving the actual times, one reported time to cecal intubation only [19] and therefore was excluded, 3 trials reported means and standard deviations,[12, 14, 18] and 2 reported medians.[16, 17] None of these studies showed a significant difference between study groups and the pooled estimate (by combining the three studies reporting means and standard deviations) did not differ between propofol sedation and usual care (Figure 3).

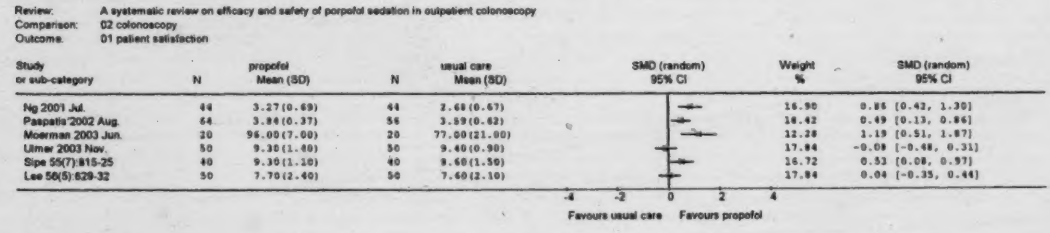
Figure 3 Procedure Time.



1.3.2. c) Patient Satisfaction

Seven trials reported this outcome.[11-15, 18, 19] Four used visual analog scales (one with a 0-100 scale, three with a 0-10 scale),[12, 13, 18, 19] and two used categorical questionnaires.[14, 15] One study was excluded because it did not report standard deviation.[11] The results on categorical questionnaires in these two studies were subsequently converted to a 4 point scale to facilitate statistical analysis as described in the methodology section. Since different scales were used to measure this outcome, it was not appropriate to combine data. However, there was a trend favoring propofol (Figure 4).

Figure 4 Patient Satisfaction.

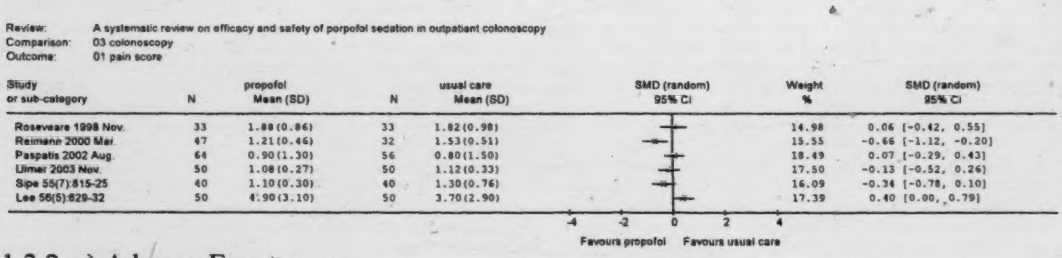


1.3.2. d) Pain Scores

Of the eight trials which reported this outcome,[11, 12, 14, 15, 17-19] four used visual analog scales (three with a scale of 0-10, and one with a scale of 0-4)[11, 12, 14, 15] and four used categorical questionnaires.[16-19] Of these eight studies, three reported means and standard

deviation,[12, 15] four reported proportion of patients in each category.[16-19] and one reported mean score at 30 minutes post procedure[14] and therefore was excluded. Again the results on categorical questionnaires were converted to a 4 point scale to facilitate statistical analysis. Since different scales were used, it was not appropriate to combine data on this outcome. However, it did not appear to demonstrate a difference between the two groups (Fig. 5).

Fig 5 Pain Scores.



1.3.2. e) Adverse Events

There was no colonic perforation in any of the studies.

Three of the ten studies reported no serious hemodynamic or respiratory complications.[11, 14, 17] Other major side effects were summarized in Table 2 below:

Table 2. Adverse events.

Adverse events	Hypotension		O_2 desaturation		Change in heart rates	
group / study	propofol	control	propofol	control	propofol	control
Paspatis	24/64 (37.5%)	17/56 (30.4%)	11/64 (17.2%)	10/56 (17.9%)	3/64 (4.7%)	2/56 (3.6%)
Ulmer	4/50 (8%)	4/50 (8%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Sipe	0/40 (0%)	2/40 (5%)	1/40 (2.5%)	0/40 (0%)	0/40 (0%)	2/40 (5%)
Lee	2/50 (4%)	14/50 (28%)	0/50 (0%)	4/50 (8%)		
Moerman			2/20 (10%)	2/20 (10%)	0 (0%)	2/20 (10%)
Reimann			19/47 (40.4%)	22/32 (68.8%)		

Four studies reported hypotension (using various definitions),[12, 15, 18, 19] with no obvious difference between propofol and traditional sedation.

Seven studies reported oxygen desaturation (using various definitions).[10, 12, 13, 15, 16, 18, 19] One of the seven studies indicated supplemental oxygen was required in a significantly higher proportion of patients in the propofol group (<0.05) but did not indicate the actual numbers in each arm.[10] One trial reported 2 cases of severe oxygen desaturation requiring ventilatory support with laryngeal mask and reversal of sedation with an antidote in the traditional sedation group, but none in the propofol group.[15]

Four studies reported significant change in heart rates compared to baseline with either bradycardia or tachycardia (using various definitions).[15, 19] Two studies reported no hemodynamic complications in any of the parcitipants.[14, 17] Overall there were no significant group differences (Figure 8).

Other minor side effects such as nausea, vomiting, dizziness or vertigo were reported as not significantly different between groups in 4 studies.[10, 12, 16, 19]

Overall, there were no significant group differences with respect to any of the reported adverse events.

1.3.2. f) Cost Analysis

Only two studies reported costs, but both focused on drug costs alone and neither included staffing or facility costs.[10, 17] Therefore, no conclusion can be drawn on this outcome.

1.4. Discussion

In summary, we found that the current evidence base for propofol sedation for routine colonoscopy consists of 10 randomized trials which have studied only 780 patients. Four of the ten studies were considered to be of high quality, with Jadad scores of at least 4. Our review focused on the following outcome measures: recovery times, procedure times, patient satisfaction, pain during procedure, and adverse events.

Of the eight trials which reported recovery time, four studies did not use any validated scale to measure this outcome. The pooled estimate suggested that propofol sedation did shorten post-procedure recovery time by 14 minutes (95% CI 10 minutes to 18 minutes). It should be noted that different scales were used to assess recovery and the only study using a validated scale for assessing patients after general anesthesia (the Aldrete scale) reported a non-significant result.[10] However, this study had compared propofol based sedation with 2 control groups: one with diazepam plus demerol and one with midazolam plus fentanyl. Thus, this study was likely under-powered to detect statistically significant differences against each control group alone. If the two control groups were combined, propofol based sedation did significantly shorten recovery time (Figure 2). However, the

validity of combining two control arms when it was not pre-specified in the analytic plan of the study is open to question.

Despite such variation among studies and methodological limitation, there is an overall trend favoring shorter recovery times in propofol based sedation. Thus, although the existing data suggests that propofol sedation does shorten post procedure recovery time without increased risks to patients compared to usual sedation, it cannot be considered definitive. Indeed, as only three of these trials used validated scales to assess post-propofol recovery time (the Aldrete scale and Observer's assessment scale), it could be argued that propofol sedation has only been compared to usual care for colonoscopy in three trials consisting of 237 patients, even though none of these assessment scales are deemed "perfect". Clearly, there is a need for further randomized trial evidence to evaluate propofol sedation.

This systematic review included only randomized controlled trials comparing propofol based sedation to usual care in colonoscopy. Other trials which included other procedures such as gastroscopy, EUS or ERCP were excluded. Propofol alone was used in 4 trials,[13, 14, 18, 19] while the remaining 6 trials combined propofol with either a benzodiazepine or an opiate. Three of these 4 trials evaluating propofol alone were reported as positive studies for recovery time. It could be argued that adding another agent with a longer half life to propofol sedation would prolong post procedure recovery times and defeat the purpose of using propofol in the first place. However, even when a second agent with a longer half life was added to propofol, 5 of the 6 trials still reported shorter recovery times with propofol sedation.

The combined data from this analysis suggest no difference between the propofol based sedation and the usual sedation with respect to procedure time, patient satisfaction or pain scores, although the quality of the data is suboptimal.

There were no major adverse events such as perforation or need for mechanical ventilation reported in the included studies, with a total 780 patients. The number of patients is certainly low and major adverse events are not expected to occur. But if one considers the total number of over 80,000 patients reported in numerous endoscopy trials using propofol based sedation,[5] one may conclude that propofol sedation is probably safe.

Currently there is a remarkable lack of data to determine whether propofol sedation in colonoscopy is cost effective. If a registered nurse or an endoscopist provides propofol sedation, it is conceivable that the cost of propofol may be offset by a shorter recovery time, reducing overall cost. However, if an anesthesiologist is required to administer propofol due to institutional policies, propofol sedation for routine colonoscopy probably is not cost effective.

The American College of Gastroenterology, the American Gastroenterological Association , and the American Society of Gastrointestinal Endoscopy issued a joint statement on sedation in endoscopy in March 2004 which indicated that "clinically

important benefits [of propofol sedation] over standard sedatives have not been consistently demonstrated in average-risk patients undergoing standard upper and lower endoscopy and further randomized clinical trials are needed".[22] This systematic review has further illustrated the need for more high quality randomized trial evidence on the efficacy of propofol sedation for outpatient colonoscopy.

Chapter 2: Study Objectives and Hypothesis

2.1. Study Objectives

The primary objective of this study was to determine if propofol sedation leads to shorter recovery time in elective outpatient colonoscopy compared to usual care.

The secondary objectives were to determine the procedure times, patient satisfaction, adverse events in outpatients receiving propofol or traditional sedation for elective colonoscopy.

2.2. Hypothesis

Propofol sedation results in shorter recovery time compared to usual care. There are no significant differences in procedure times, patient satisfaction and adverse events between the two groups.

Chapter 3: Methods

3.1 Study Design

This prospective randomized study compared propofol sedation with midazolam plus meperidine (M + M) in routine outpatient colonoscopy. Five endoscopists and three anesthesiologists participated in this study. The primary outcome was recovery time and was assessed by a single individual blinded to treatment allocation. The research participants were blinded if they had no prior experience with colonoscopy since they had no prior knowledge of the various agents used for sedation (ie propofol is white whereas midazolam and meperidine are colorless). The endoscopists and anesthesiologists were not blinded to group allocation.

3.2 Setting

This study was conducted at the University of Alberta Hospital as a collaboration between the Division of Gastroenterology and the Department of Anesthesiology between Feb 14 and June 13, 2006. The study protocol was approved by the U of A Health Research Ethics Board (#6051).

3.3 Study Population

Consecutive adult outpatients who required routine colonoscopy by the five endoscopists were recruited to participate in this study.

3.3.1 Inclusion Criteria: 1) age >18 and 2) elective colonoscopy.

3.3.2 Exclusion Criteria: 1) allergy to study medications (propofol, midazolam, and meperidine), eggs or soybean (constituents of propofol); 2) history of colonic resection; 3) inability to understand spoken/written English; 4) dementia; 5) pregnancy; and 6) unwillingness to participate in the study.

3.4 Trial Interventions

Intravenous sedation was administered by one of the three anesthesiologists. Patients in the intervention group received intravenous propofol boluses. The initial bolus was 40 mg. Additional boluses of 10 mg were given as needed. Patients in the control group received intravenous midazolam and meperidine boluses. The starting doses of midazolam and meperidine were 3 mg and 50 mg, respectively. Additional boluses were given as needed. All patients were sedated to level 1 or 2 on Observer's Assessment scale (Appendix A). The doses of medications each patient received were recorded.

3.5 Randomization Method

Randomization was conducted in blocks of 4 using a random number generator and stratified by endoscopists with allocation of concealment maintained through the use of serially numbered sealed opaque envelopes.

3.6 Primary and Secondary Outcome Measures

3.6.1 Primary Outcome

The primary outcome was recovery time. Since no validated scale existed to assess readiness for discharge following conscious sedation in this setting, full recovery was defined by 4 criteria: 1) score of 10/10 on the Aldrete's scale; 2) score of 5/5 on Observer's assessment scale; 3) ability to complete serial 7 subtractions; and 4) ability to stand and walk independently.

As discussed in Chapter 1, the Aldrete scale (Appendix A) was developed in 1970 by an anesthesiologist and was prospectively validated in assessing readiness to be discharge from the operating room.[20] A minimum score of 8/10 indicated that the patient was safe to retrun to the ward. Since propofol, a general anesthetic, was used in this trial, this scale was chosen and a score of 10/10 was required to satisfy one of the recovery criteria.

The Observer's assessment scale (Appendix A) was validated for benzodiazepine sedation and was chosen since midazolam was one of the study drugs.

Each patient was assessed at 10 minute intervals by a single binded outcome assessor until all 4 criteria had been met.

3.6.2 Secondary Outcomes

1) Procedure time: defined by the time when sedation was given until the endoscope was withdrawn. This was measured and recored in 3 segments by an endoscopy nurse who assited with the procedure:
    a. Time to sedation: defined by the time interval between sedation administration and scope insertion.
    b. Time to cecal intubation: defined by the interval between scope insertion to cecal intubation.
    c. Withdrawal time: defined by the interval between cecal intubation to scope withdrawal.
2) Patient satisfaction: assessed by a visual analog scale of 1-10 with 1 being lowest satisfaction and 10 being highest satisfaction.
3) Adverse events: hypotesion (defined as systolic BP< 85 mmHg lasting for more than 1 min), oxygen desaturation (< 85% on 2L/min of oxygen lasting more than 1 min), need for intubation or mechanical ventilation, and colonic perforation.

3.7 Data Collection

Baseline characteristics including gender, age, height and weight were collected by a questionnaire administered to patient prior to colonoscopy. During the procedure, an endoscopy nurse assisting with colonoscopy recorded procedure time, and the need for biopsy or polypectomy. Each anesthesiologist recored the doses of sedatives each patient received. Following colonoscopy, the outcome assessor collected data on recovery times and administered a second questionnaire on patient satisfaction prior to discharge.

3.8 Sample Size Calculation

The recovery time was our primary outcome and thus used determine sample size. A statistical software program was used (Power and Sample Size calculator, University of Vanderbilt, USA, available at http://biostat.mc.vanderbilt.edu) to calculate sample size by using the previously reported mean recovery times[10] of 13.3 min (15.7) and 25 min (29.9) for propofol and midazolam plus meperidine, respectively. A sample size of 20 per arm was estimated to be needed to detect (or exclude with 80% power at a two sided alpha of 0.05) a 30 min difference, which was judged to be clinically significant by a concensus within our GI division. To account for attrition and the possibility of the standard deviations being larger than seen in the Kostash study, we expanded the sample size to 92 patients, since randomization was conducted in blocks of 4.

3.9 Planned Analysis:

Demographic and baseline characteristics of patients were analyzed by descriptive methods. The primary outcome (recovery time) was analyzed according to the intention-to-treat principle. We planned to compare the mean recovery times between the propofol and control groups by using the student's t test if the recovery times were normally distributed or the Mann-Whitney test if this outcome was not normally distributed. A p value of less than 0.05 was considered significant. Total procedure times and patient satisfaction were also analyzed by the student's t test or Mann-Whitney test depending on whether normality was satisfied. Adverse events were analyzed by descriptive methods. No interim analyses were planned.

3.10 Ethics

The study protocol was approved by the Health Research Ethics Board of the University of Alberta, Edmonton. Copies of the information sheet, consent form, and data collection forms were included as Appendices B, C and D. This trial did not receive industry funding.

Chapter 4: Results

4.1. Demographics and Descriptive Statistics

Ninety two patients were enrolled in this study. Forty five patients were randomized to the propofol group and 47 patients to the control group. The percentage of male patients was 62% in the propofol group and 47% in the control group. Other baseline characteristics such as age and BMI were similar between groups. Approximately 50% of patients had previous colonoscopy in both groups (Table 3). No patients were lost to follow up.

Table 3. Patient Baseline Characteristics

	Propofol	Control	P
Number of patients	45	47	
Gender			
Male (%)	28 (62%)	22 (47%)	0.141
Female (%)	17 (38%)	25 (53%)	
Mean age (SD)	56.7 (10.8)	56.4 (13.6)	0.243
Mean BMI (SD)	26.8 (5.2)	26.7 (5.9)	0.896
Previous colonoscopy (%)	22 (49%)	25 (53%)	0.488

The median dose of propofol in the propofol group was 180 mg. The median doses of midazolam and meperidine in the control group were 4 mg and 100 mg respectively (Table 4).

Table 4. Doses of Sedatives by Groups (Median and Interquartile range(IQR)).

Median (IQR)	Propofol (N=45)	Control (N=47)
Propofol (mg)	180 (150-250)	
Midazolam (mg)		4 (3-5)
Meperidine (mg)		100 (75-100)

4.2 Primary and Secondary Outcomes

4.2.1 Primary Outcome: Recovery Time

Recovery time was not normally distributed for either the propofol or control groups (Figures 6 and 7, $p<0.001$). Eighty five percent of patients in the propofol group reached full recovery, as defined in Chapter 3, in less than 25 minutes whereas 83% of patients in the control group required greater than 25 minutes after colonoscopy.

Figure 6. Recovery Time Histogram in Propofol Group.

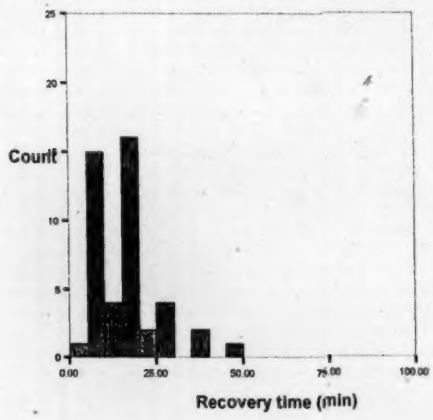
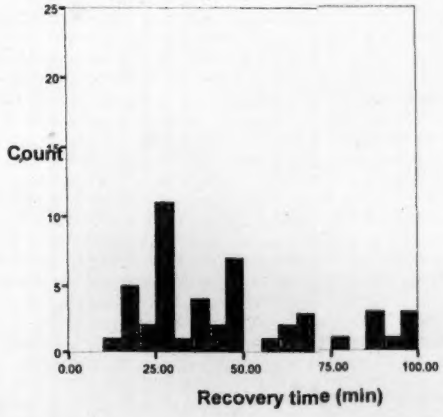


Figure 2. Recovery Time Histogram in Control Group.



Since recovery time was not normally distributed, the Mann-Whitney test was used for the primary analyses and demonstrated significantly shorter recovery time in the propofol group compared to the control group ($p<0.001$) (Table 5).

Table 5. Primary and Secondary Outcomes

Median (IQR)	Propofol	Control	P
Recovery time (min)	20.0 (10-30)	45.0 (7.5- 82.5)	<0.001
Procedure time (min)	13.0 (10-19.5)	15.0 (12.75-22)	0.082
Withdrawal time (min)	5.0 (3-8.5)	7.13 (3-9.5)	0.599
Biopsy	11 (24%)	10 (21%)	0.806
Polypectomy			
No polyp	33 (73%)	31 (66%)	0.329
1 polyp	3 (7%)	11 (23%)	0.026
2 polyps	6 (13%)	3 (6%)	0.265
3 polyps	3 (7%)	2 (4%)	0.612
Patient satisfaction	10 (10-10)	10 (9.75-10)	0.984
Adverse events			
Perforation	0	0	
Intubation	0	0	
Transient hypotension	2 (4%)	1 (2%)	0.585
Transient O_2 desaturation	1 (2%)	1 (2%)	0.975

The recovery time was also examined by each individual assessment scale as shown in figure 8-15. The results were consistent with the above findings that recovery time was significantly shorter in propofol group compared to the control group ($p<0.001$ for all four assessment tools).

Figure 8. Recovery Time (by Aldrete's Scale) Histogram in Propofol Group.

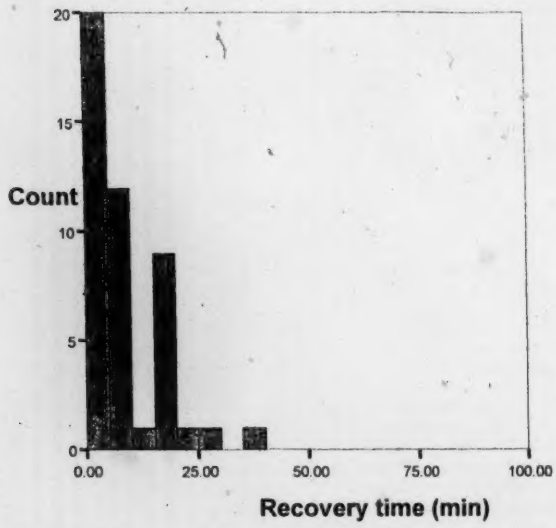


Figure 9. Recovery Time (by Aldrete's Scale) Histogram in Control Group.

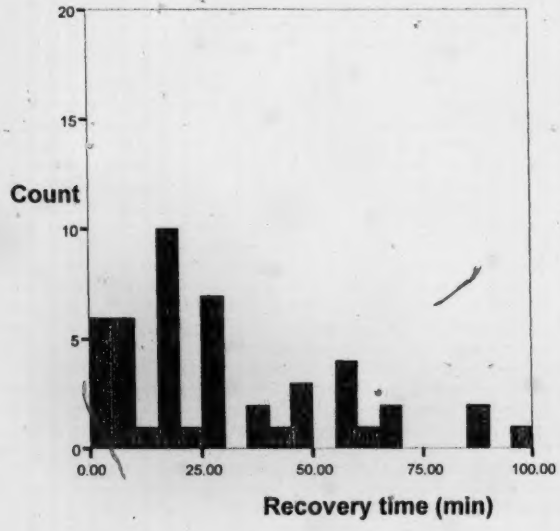


Figure 10. Recovery Time (by Observer's Scale) Histogram in Propofol Group.

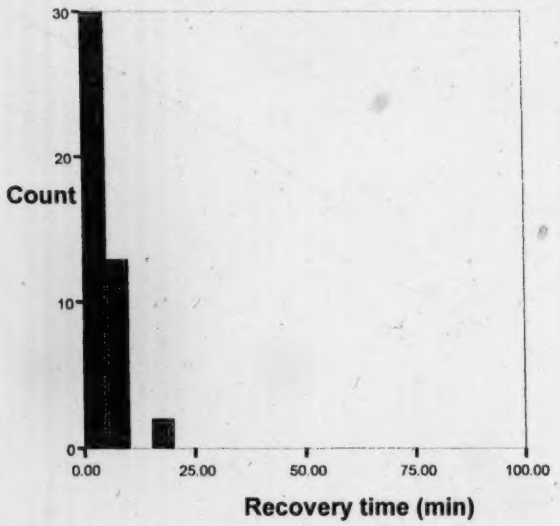


Figure 11. Recovery Time (by Observer's Scale) Histogram in Control Group.

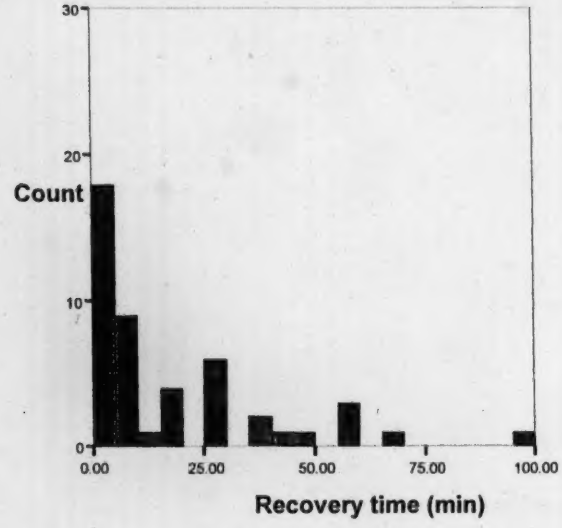


Figure 12. Recovery Time (by Serial 7 Subtractions) Histogram in Propofol Group.

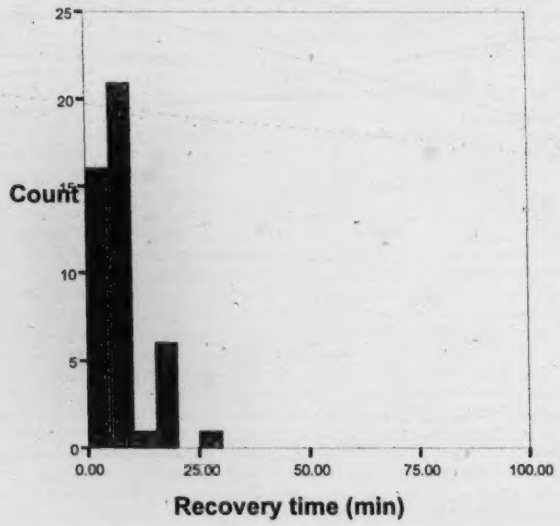


Figure 13. Recovery Time (by Serial 7 Subtractions) Histogram in Control Group.

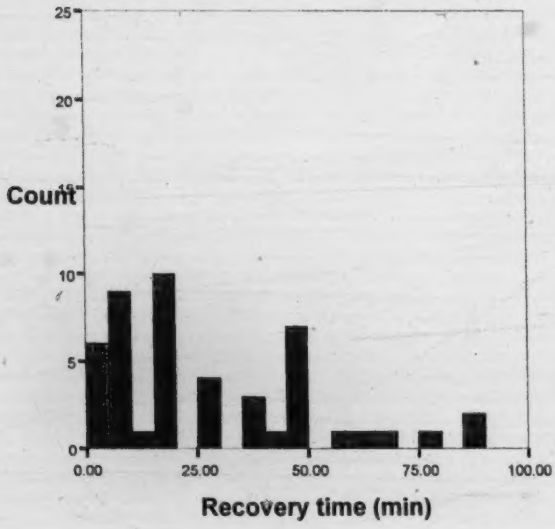


Figure 14. Recovery Time (by Ability to Stand and Walk Independently) Histogram in Propofol Group.

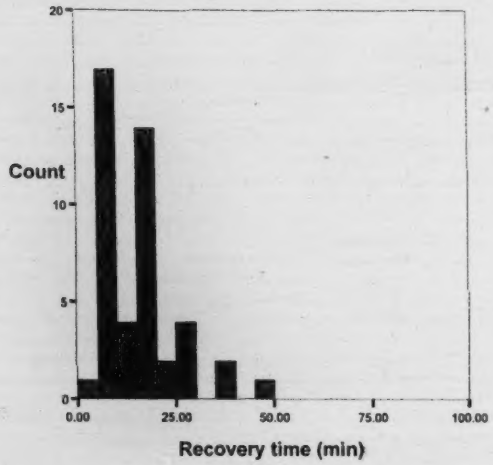
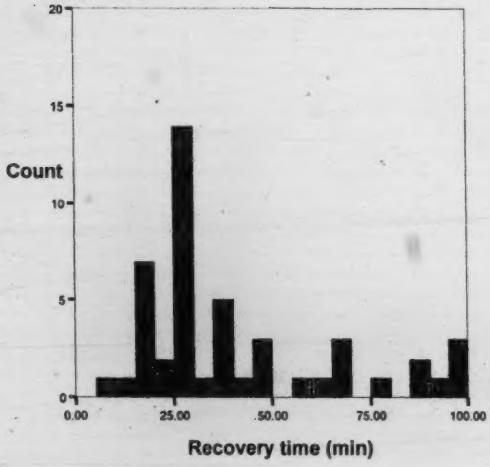


Figure 15. Recovery Time (by Ability to Stand and Walk Independently) Histogram in Control Group.



4.2.2 Secondary Outcomes

4.2.2.1 a) Total Procedure Times

Total procedure times were not normally distributed (Table 5). Ninety eight percent of colonoscopies in the propofol group and 94% in the control group were completed within 30 minutes (Figures 16 and 17). The proportions of patients who required colonic biopsy or polypectomy were not significantly different between the two groups (Table 5).

Figure 16. Total Procedure Time Histogram in Propofol Group.

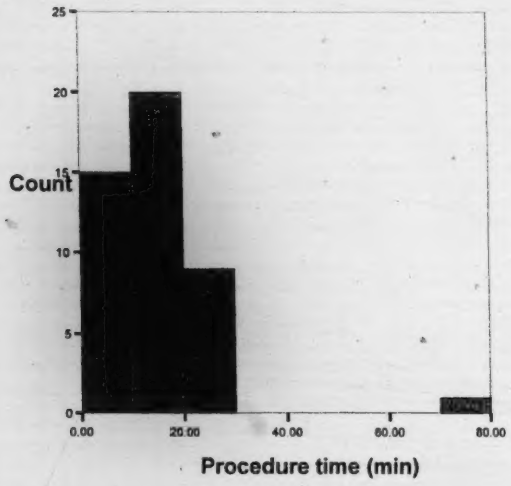
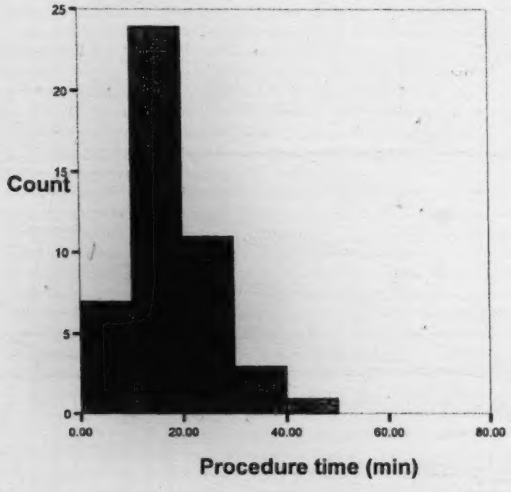


Figure 17. Total Procedure Time Histogram in Control Group.



Mann-Whitney test demonstrated no significant differences in the total procedure times between groups (p= 0.082).

4.2.2.1. b) Sedation onset times

Times to sedation onset were not normally distributed. Overall time to sedation was significantly shorter in the propofol group than the control group (p= 0.003). The medians (IQR) were 2 minutes (1-2) and 2 (2-4) minutes for propofol and control groups respectively. Colonoscopy commenced within 3 minutes of sedation administration in

96% of patients in the propofol group compared to 72 % of patients in the control group (Figures 18 and 19).

Figure 18. Time to Sedation Histogram in Propofol Group.

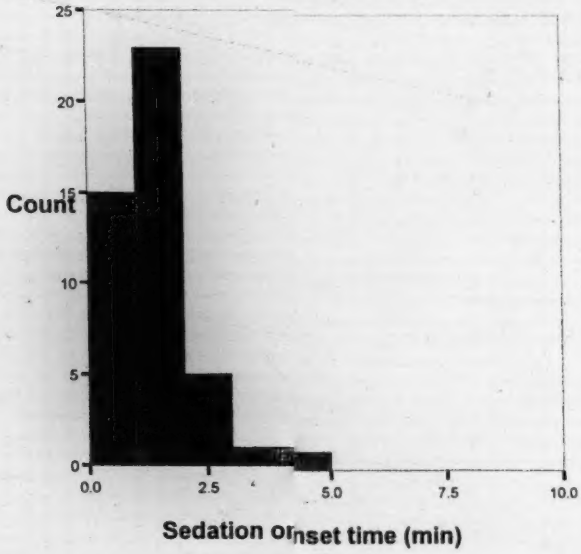
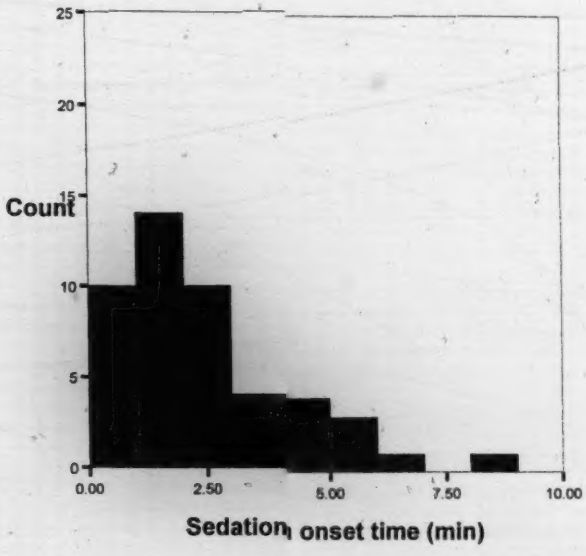


Figure 19. Time to Sedation Onset in Control Group.



4.2.2.1.c) Withdrawal Times

Withdrawal time of less than 5 minutes was seen in 64% of colonoscopies in propofol group and 62% in the control group. There was no significant group difference (p=0.767).

Figure 20. Withdrawal Time Histogram in Propofol Group.

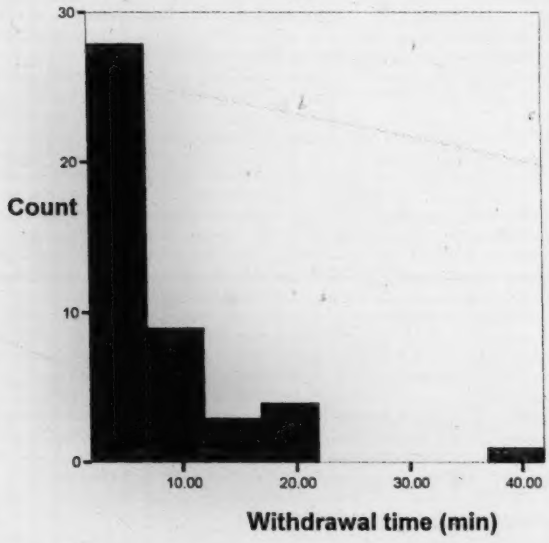
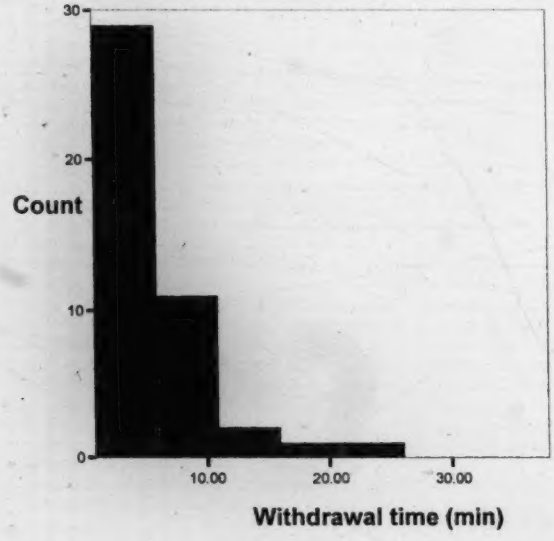


Figure 21. Withdrawal Time Histogram in Control Group.



4.2.2.2 Patient Satisfaction

Patient satisfaction scores were not normally distributed but were high in both groups. Mann-Whitney test did not demonstrate a significant difference between groups (p= 0.861).

Figure 22. Patient Satisfaction Histogram in Propofol Group.

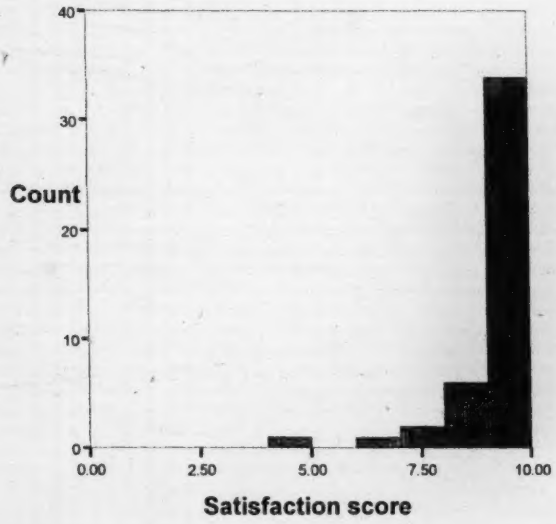
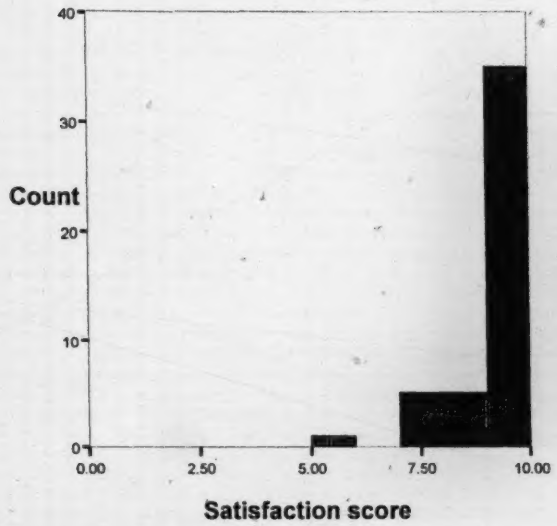


Figure 23. Patient Satisfaction Histogram in Control Group.



4.2.2.3 Adverse Events.

There were no cases of colonic perforation or need for mechanical ventilation. One patient in each group had transient oxygen desaturation during the procedure and responded to supplemental oxygen. Two patients in the propofol group and 1 patient in the control group had transient hypotension which resolved spontaneously. There were no significant group differences in these outcomes (Table 5).

Chapter 5 Discussion

In this study, we found that the median recovery time was significantly shorter in the propofol group than the midazolam and meperidine group (20 minutes compared to 45 minutes, $p<0.001$). This difference is explained by the pharmacokinetics of the drugs, with propofol having the shortest half life. The median total procedure times were 13 minutes and 15 minutes in the propofol and midazolam plus meperidine groups respectively, and were not significantly different ($p=0.082$). As expected, adverse events were infrequent in both groups in this trial, given the relatively small number of participants. The patient satisfaction with regards to sedation was not statistically different between the two groups. These findings are in agreement with the results presented in our literature review in Chapter 1.

A priori we expected to find a shorter recovery time with propofol than the combination of midazolam and meperidine. Indeed, we found that propofol sedation reduced the recovery time by 25 minutes compared to conventional sedation. Even though this is 5 min less than our consensus of 30 min as the minimal clinically significant difference pre-specified by our Division of Gastroenterology, we still think it is clinically relevant, since it does have cost saving potentials, as discussed below.

The primary outcome was recovery time. As was discussed in Chapter 3, there is no universally accepted scale to evaluate "full recovery" after colonoscopy. We wanted to use a tool that was easy to administer and could quickly identify a patient's return to neuropsychological baseline after an uncomplicated procedure. To achieve this, we decided to use a combination of four criteria: 1) Aldrete's scale, 2) Observer's scale, 3) serial seven subtractions, and 4) ability to stand and walk independently. Aldrete's scale is a validated tool which assesses a patient's vital signs, level of consciousness and ability to move extremities after general anesthesia. The Observer's scale is a validated scale which assesses a patient's level of responsiveness after benzodiazepine sedation (ie respond readily to name, response to name, respond only when called loudly and repeatedly, etc.). However, each of the two scales alone is inadequate to accurately assess many of neuropsychological functions essential for daily activities, such as the ability to walk, reason or remember. Although the combination of these four criteria has not been previously validated for assessing recovery in this setting, we felt that it allowed us to better define full recovery and became the greatest strength of our study.

Withdrawal phase is considered to be the most important aspect of colonoscopy during which an endoscopist looks for mucosal abnormalities and performs necessary therapeutic interventions. It is generally agreed that the more time an endoscopist spends examining the colonic mucosa, the more neoplastic lesions will be detected. The duration of withdrawal time also increases if biopsy or polypectomy is required. A study published in 2006 found that endoscopists who spent at least six minutes during the withdrawal phase have a significantly higher rate of polyp detection at 28% compared to those who spent less than six minutes at 11%. Therefore the authors recommended that six minutes should be the minimum amount of withdrawal time.[23] Since the percentages of biopsy and polypectomy were similar in both sedation groups, we anticipated that withdrawal

time would be similar in both groups and indeed the median withdrawal times were 5 minutes in the propofol group and 7 minutes in the midazolam plus meperidine group (P=0.599). In our study, the withdrawal times were less than 5 minutes in about 60% of all cases and were not significantly different between groups. This fell short of the six minute minimum recommendation. Many people have argued that it is not the absolute amount of time spent withdrawing the scope that determine the adenoma detection rate, but rather the skills and carefulness of the endoscopists who perform the procedure.[24, 25] The polyp detection rates of 27% (propofol group) and 34% (control group) in our study were well within the reported polyp detection rates of 20-30% in large clinical studies.[26, 27] Perhaps the optimal withdrawal time is not an absolute number, but it rather depends on both patient factors (indication for procedure, quality of bowel preparation, or previous colonic resection), as well as physician factors (diligence and skills of the endoscopist).

Patients did not seem to prefer one sedation regimen over the other in our study. However, one could argue that their perception of sedation and procedure may be clouded due to a euphoric effect from the sedatives, and that a better time to administer the questionnaire is a day after the procedure when they can more critically evaluate their experiences.

The current standard sedation for elective endoscopic procedures at the University of Alberta Hospital is the combination of midazolam and meperidine. Propofol can only be administered by an anesthesiologist. It is usually reserved for difficult cases or when a patient is unable to tolerate standard sedation. After a procedure, each patient is taken from the endoscopy suite to the dayward for recovery, where he or she is monitored for at least an hour or until he or she is deemed "safe" (i.e. able to verbally respond, drink and walk) to be discharged. In our study, the median recovery time for midazolam plus meperidine was 45 minutes, which is 15 minutes shorter than what the current discharge policy dictates as the minimal amount of detention time after a procedure. This means that some patients are kept longer unnecessarily after endoscopy. Moreover, the median recovery time for propofol was 20 minutes, which is 40 minutes shorter than the current minimal detention time, and 25 minutes shorter than the median recovery time for our standard sedation. This twenty-five minute difference could translate into savings of approximately $142,000 dollars per year, given that the average operating cost of our dayward is $130 per hour and 2623 outpatient colonoscopies were performed at the University of Alberta in 2005.[28]. The difference in drug costs is not significant, averaging $1.61 per patient. However, the cost of anesthesiologists administering propofol is also substantial at $100 per 30 minutes, which would amount to $131,150 per year. Therefore we will not realize significant cost savings since propofol sedation is currently limited to the anesthesiologists. On the other hand, substantial savings could be achieved if 1) propofol sedation can be administered by non-anesthesiologists and 2) a new discharge policy is established based on each patient's recovery speed, not by a preset time parameter.

A recent survey of endoscopists in the United States reported that 68% of those who use conventional sedation would consider using propofol sedation provided adequate staff

training and additional safety measures can be instituted at a reasonable cost.[29] However, there continues to be significant controversy and debate over the use of propofol sedation in routine endoscopy by non-anesthesiologists. Studies examining a non-anesthesiologist model with more than 80,000 accumulated patients safely sedated using propofol have concluded that there is no increased sedation related mortality compared to traditional sedation, provided that specific training has taken place.[5] The anesthesiology community continues to express patient safely concerns about propofol sedation administered by non-anesthesiologists,[5] and in fact, non anesthesiologists are not allowed to administer propofol in many institutions. Furthermore, if an anesthesiologist is required to administer propofol, the cost of the procedure will rise substantially. These factors have prevented widespread adoption of propofol sedation for routine endoscopic procedures.

In conclusion, propofol sedation appears to be superior to traditional sedation with meperidine plus midazolam in regard to recovery profile for routine colonoscopy. However, in most instances by institutional policies, propofol sedation still needs to be administered and monitored by anesthesiologists who are in short supply. If an anesthesiologist attends to every colonoscopy, the cost of each procedure will also increase substantially. Therefore, the feasibility of propofol sedation in routine, elective endoscopy is currently uncertain. As demonstrated in our study, there are potentially significant cost savings that may be realized by using propofol sedation due to shorter recovery times. Efforts to train non-anesthesiologists to administer and monitor propofol provide an option which increases the feasibility of propofol sedation in routine endoscopy. Future studies on economic analysis of propofol sedation in outpatient colonoscopy may demonstrate benefits beyond shorter recovery times.

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Appendix A.

Aldrete Recovery Scale

Category	Description	Score
Consciousness	Fully awake and oriented (name, place, date) Arousable on calling Not responding	2 1 0
Activity	Moves all 4 extremities voluntarily or on command Moves 2 extremities Unable to move extremities	2 1 0
Respiration	Breathes deeply and coughs freely Dyspnea, limited breathing, or tachypnea Apneic or on mechanical ventilation	2 1 0
Circulation	Blood pressure +/- 20% of preanesthetic level Blood pressure +/- 20%-49% of preanesthetic level Blood pressure +/- 50% of preanesthetic level	2 1 0
Oxygen saturation	$SpO_2 > 92\%$ on room air Supplemental O_2 required to maintain $SpO_2 > 90\%$ $SpO_2 < 92\%$ with O_2	2 1 0
Max score		10

Observer's Assessment of Alertness/Sedation Scale (OAA/S)

Responsiveness	**Score**
Respond readily to name	5
Lethargic response to name	4
Respond only when called loudly and/or repeatedly	3
Respond only after mild prodding and/or shaking	2
Does not respond to mild prodding and/or shaking	1

Appendix B.

PATIENT INFORMATION SHEET

Title of Research Study: A Randomized Controlled Trial Comparing Propofol Sedation with Usual Care in Routine Colonoscopy

Principal Investigators: Dr. Finlay McAlister, Dr. Dina Kao, Dr. Richard Fedorak, Dr. Eoin Lalor, Dr. Gurpal Sandha & Dr. Jeff Johnson

Background: You are scheduled to have a colonoscopy. The usual practice is to give a combination of 2 drugs: a sedative (eg. Versed) and a painkiller (eg. Demerol) during the procedure. These medications will make you feel relaxed, sleepy and free of pain. After the procedure, you will need some time to recover because these drugs take a while to break down and leave your body.

We would like to try another drug, propofol, for sedation. It takes much less time to break down and therefore you may recover faster and leave the hospital sooner. It may also be more comfortable for you during the procedure because you get deeper sedation compared to the usual combination.

Purpose: We are conducting this study to compare the two different ways of sedation to see if indeed propofol works better. One hundred and two people undergoing colonoscopy will take part in this study.

Procedure: Once you have agreed to participate, you will be randomly assigned to receive either the usual combination or propofol sedation for your colonoscopy. This is done by a flip of a coin. You cannot decide which drug you will receive.

If you are assigned to the propofol group, you will not need a painkiller since propofol itself provides a very deep level of sedation that you will not feel pain without a painkiller.

Following colonoscopy, a physician will assess the speed of your recovery by asking you questions to test your memory and concentration. You will also fill out a questionnaire describing how satisfied or unsatisfied you are with the sedation. You will also receive a phone call 24 hours after your procedure to see if you have returned to your daily activities.

Potential benefit: If you receive propofol, you may feel less pain during colonoscopy. You may also leave the hospital sooner after your procedure.

Title of Research Study: A Randomized Controlled Trial Comparing Propofol Sedation with Usual Care in Routine Colonoscopy

Potential harm: If you receive propofol, there is a very small chance that you may stop breathing because you are deeply sedated. The effect is only temporary and will reverse within minutes. This can also happen if you receive the usual combination for sedation.

If this happens, you will not receive further doses of propofol and another physician will push air into your lungs with a mask. Again, the effect is only temporary and once the drug wears off, you should be able to breathe on your own again.

Confidentiality: Personal records relating to this study will be kept confidential. Only the principal investigators will have access to your personal data. Once the study has completed, the data will be deleted.

Voluntary Participation: You do not have to participate in this study. You are free to withdraw from the research study at any time prior to the drug(s) being given, and your continuing medical care will not be affected in any way.

Compensation for Injury: If you become ill or injured as a result of participating in this study, necessary medical treatment will be available at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Contact Names and Telephone Numbers:

If you have any questions about the study, you can ask your doctor, the study nurse or Dr. D. Kao (pager 445-7081).

If you have concerns about your rights as a study participant, you may contact the Patient Relations Office of Capital Health, at 407-1040. This office has no affiliation with the study investigators.

If you agree to participate in this study, please sign the enclosed consent form and bring it with you when you come for your colonoscopy.

Appendix C.

CONSENT FORM

Title of Project: A Randomized Controlled Trial Comparing Propofol Sedation with Usual Care in Routine Colonoscopy

Principal Investigators: Dr. Dina Kao Phone Number: 492-8307
Co-Investigators: Dr. R. Fedorak, Dr. E. Lalor, & Dr. G. Sandha

To be completed by the research subject:

	Yes	No
Do you understand that you have been asked to be in a research study?	___	___
Have you read and received a copy of the attached Information Sheet?	___	___
Do you understand the benefits and risks involved in taking part in this research study?	___	___
Has the issue of confidentiality been explained to you?	___	___
Do you understand who will have access to you records, including personally identifiable health information?	___	___
I agree to take part in this study:	___	___

Signature of Research Subject: _____

Printed Name: _____

Date: _____

Signature of Witness: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator: _____ Date: _____

Appendix D.

Endoscopy room data sheet

Patient study ID _____
Date of study ____/_____/_____ (month/day/year)

1. **Group assignment**:

Propofol _____ mg

OR

Usual care: Versed _____ mg Demerol _____ mg

2. **Time**:

Time when sedation is given _____:_____
Time when procedure starts (rectal intubation) _____:_____
Time when cecum is intubated _____:_____
Time when procedure is terminated (scope withdrawn from patient) _____:_____
Biopsy Yes ___ No ___
Polypectomy Yes ___ No ___ Number of polyps _____

3. **Adverse events during procedure**:

Need for intubation or ventilation Yes _____ No _____
Need for antidote to reverse sedation Yes _____ No _____
Arterial desaturation during procedure Yes _____ No _____
Hypotention during procedure Yes _____ No _____

Recovery room data sheet

Patient study ID _____
Date of study ____/____/_____ (month/day/year)

Arrival time at recovery room _____: _____

Aldrete score (max 10/10) AND **Observer's Assessment Scale** (max 5/5)

When patient arrives at recovery room _____/10 and _____/5

10 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
20 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
30 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
40 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
50 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
60 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
70 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
80 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
90 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
100 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
110 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5
120 min after arrival _____/10 AND Serial 7's: ____93, _____86, ____79, ___72, ____65, _____58 AND _____/5

Amount of time required for patient to reach 10/10 on Aldrete's and Observer's assessment scale and completed serial 7's following arrival at recovery room: _____ min

Time when patient is discharged from recovery room _____: _____

2. **Adverse events**:

Need for intubation or ventilation	Yes ____ No ____
Need for antidote to reverse sedation	Yes ____ No ____
Arterial desaturation	Yes ____ No ____
Hypotension	Yes ____ No ____

Patient data sheet

Patient study ID _____
Date of study ____/_____/_____ (month/day/year)

Pre procedure

1. Age: _____

2. Gender: M ___ F ____

3. What is your height _____feet ____ inches OR _____ cm

4. What is your weight _____ lb OR _____ kg

5. Alcohol consumption: 5 or more drinks per day _____, less than 5 drinks per day _____, no alcohol _____

6. Use of narcotics/pain killers (eg. Morphine, Demerol):
Yes ____ . Please specify name of drug: _____ , daily dose: _____ mg per day duration _____ days/weeks/years (please circle a response).
No ____

7. Use of benzodiazepine/sedatives/sleeping pills (eg. Ativan):
Yes ____. Please specify name of drug: _____ , daily dose: _____ mg per day and duration _____ days/weeks/years (please circle a response).
No ____

8. Previous experience with colonoscopy:
Yes ____. Number of times _____. When _____.
No ____

Post procedure

1. How satisfied are you with the procedure today with respect to sedation? Please circle a response (1= least satisfied, 10= most satisfied).
1 2 3 4 5 6 7 8 9 10

2. If you need to have this procedure repeated in the future, would you like to have the same drug for sedation again?
Yes ___
No ___. Please specify reason: _____
_____
_____
_____